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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
SHEN, WU CHENG WINSTON	
ART UNIT	PAPER NUMBER
1632	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	03/16/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/501,289	PETERSEN ET AL.	
	Examiner	Art Unit	
	Wu-Cheng Winston Shen	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 January 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-13 and 15-31* is/are pending in the application.

4a) Of the above claim(s) *19-31* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-13 and 15-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This application 10/501,289 filed on June 29, 2005 is a 371 of PCT/EP03/00518 filed on 01/16/1003, and priority of foreign application DENMARK PA 200200079 filed on 01/17/2002.

Election/Restriction

1. Applicant's election with traverse of Group I drawn to claims 1-18 in the reply filed on Jan. 24, 2007 is acknowledged. The traversal is on the ground(s) that the stem cells described by U.S. 5,650,317 are markedly different from the claimed isolated cell that there is no resemblance between them. Applicants also disagree with the examiner's characterization in the action of the subject matter of the restriction groups. However, no further argument by applicants is provided in this regard. This is not found persuasive because the common technical feature in all groups, as stated in claims 1 and 17, is an isolated cell derived from luminal epithelial cells of a mammary gland, which is capable of proliferating and differentiating into cells of mammary luminal epithelial and myoepithelial cell lineages (i. e. bi-potent mammary gland tissue cell stated in claim17). Chang et al. (U.S. Patent No: 5,650,317) teaches human breast epithelial cell type with stem cell and luminal epithelial cell characteristics, which is encompassed by the isolated cells recited in claims 1 and 17 of instant application. It is noted that the presence (or absence) of a specific marker in the recited cells is not recited in claim 17 of instant application, thereby, the markers are not part of common technical feature among all groups. Furthermore, the presence of a specific marker is considered as the inherent properties of the recited epithelial stem cell regardless whether the specific marker is disclosed in the prior arts. According, claims

19-31 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim.

In the reply filed on Jan. 24, 2007, Applicants elected a primate cell with regard to election of species of claim 13, and Applicants cancelled claim 14.

The requirement is still deemed proper and is therefore made FINAL.

Status of claims: Claims 1-13, and 15-18 are currently under examination.

Claim Objections

2. Claims 2-13, 15, and 18 are objected to because of the following informalities: It is noted that claims 2-13, and 15 depend from claim 1; therefore, the phrases "A cell" and "An immortalized cell" recited in claims 2-13, and 15 should recite "The cell" and "The immortalized cell". Based on the same reason, claim 18 depends from claim 17; therefore, the phrase "A method" recited in claim18 should recite "The method". Appropriate correction is required.

Claim Rejection - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claim 16 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the

specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Enablement is considered in view of the Wands factors (MPEP 2164.01(a)). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (*Wands*, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (*Wands*, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case is discussed below.

The following rejection under 35 U.S.C. 112, first paragraph relates to deposit requirements:

Claim 16 is directed to the immortalized cell line derived from the cell of an isolated cell derived from luminal epithelial cells of a mammary gland which is capable of proliferating and differentiating into cells of mammary gland luminal epithelial and myoepithelial cell lineages said isolated cell being capable of forming a cell culture comprising cells which are positive

staining for the luminal epithelial marker ESA (ESA+) and negative staining for sialomucin (MUC-), so-called (ESA+/MUC-) cells, wherein the said immortalized cell line is deposited in accordance with the provisions of the Budapest Treaty on the International Recognition of the Deposit of Microorganisms for the Purposes of Patent Procedure at Deutsche Sammlung von Mikroorganismen und Zellkulturen GmbH (DSMZ) and has obtained the accession number DSM ACC 2529.

It is apparent that the immortalized cell line with accession number DSM ACC 2529 is required to practice the claimed invention. As a required element, it must be known and readily available to the public or obtainable by a repeatable method set forth in the specification. If the deposit was made under the provisions of the Budapest Treaty, then an affidavit or declaration to that effect is required. See 37 CFR 1.801-1.809.

In addition to the conditions under the Budapest Treaty, applicant is required to satisfy that all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent in U.S. patent applications.

Although the claimed immortalized cell line with accession number DSM ACC 2529 is on deposit with the Deutsche Sammlung von Mikroorganismen und Zellkulturen GmbH (DSMZ), there appears no assurance as indicated above. Applicant's provision of these assurances through the submission of an appropriate declaration would obviate this rejection.

Applicants should also provide statement corroborating that the biological material deposited is a biological material specifically identified in the specification and a statement of viability from the depository.

Claim Rejection - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

4. Claims 1-3, 5, 17 and 18 are rejected under 35 U.S.C. 102(b) as being anticipated by Stingl et al. (Stingl et al., Phenotypic and functional characterization in vitro of a multipotent epithelial cell present in the normal adult human breast. *Differentiation.* 63(4): 201-13, 1998; listed as the last reference in the Information Disclosure Statement filed on 11/5/2004 by the applicants).

Stingl et al., teach phenotypic and functional characterization *in vitro* of a multipotent epithelial cell present in the normal adult human breast (See title, Stingl et al., 1998). More specifically, Stingl et al. teach the method for isolation of multipotent epithelial cell from mastectomy samples and normal tissue from reduction mammoplasties minced and dissociated in medium, which reads on isolated cells *derived from* luminal epithelial cell of a mammary gland (claim 18 of instant application), and suprabasal luminal epithelial cell of the mammary gland (claim 2 of instant application) (See lines 1-4, right column, page 202, Stingl et al., 1998).

With regard to the isolated cell and the method of isolation of said cells (claims 1, 17-18 of instant application), Stingl et al. teaches a method of isolation and characterization of *human breast epithelial cells (HBEC) with progenitor activity* by flow cytometry and single cell sorting to analyze the distribution of cellular phenotypes in primary cultures. Stingl et al. isolated two

distinct types of HBEC progenitor populations to be distinguished on the basis of their differential expression of the MUC-1 glycoprotein, and epithelial-specific antigen (ESA). One type of HBEC progenitor populations is present in the MUC-$1^{-to\ +/-}$/ ESA^{+} subpopulation, which generated mixed colonies of both luminal and myoepithelial cells. When cultured in a collagen matrix, these *bipotent progenitors* generated large branched colonies composed of a heterogeneous population of cells, with some of the progeny cells expressing luminal epitopes (keratin 8/18, *keratin 19* and MUC-1) and others expressing myoepithelial epitopes (keratin 14 and CD44v6). The MUC-$1^{-to\ +/-}$/ ESA^{+} progenitors identified and characterized by Stingl et al. are candidate ductal progenitors *in vivo* (See abstract and introduction, Stingl et al., 1998).

Thus, Stingl et al. clearly anticipates the claims 1-3, 5, 17 and 18 of instant invention.

Claim Rejection - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. Claims 1, 4, 6-13, and 15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Stingl et al. (Stingl et al., Phenotypic and functional characterization in vitro of a multipotent epithelial cell present in the normal adult human breast. *Differentiation.* 63(4): 201-13, 1998; listed as the last reference in the IDS filed by the applicants) taken with Wazer et al. (Wazer et

al., Immortalization of distinct human mammary epithelial cell types by human papilloma virus 16 E6 or E7. *Proc Natl Acad Sci U S A.* 92(9): 3687-91, 1995).

Stingl et al., teach phenotypic and functional characterization in vitro of a multipotent epithelial cell present in the normal adult human breast (See title, Stingl et al., 1998). More specifically, Stingl et al. teach the method for isolation of multipotent epithelial cell from mastectomy samples and normal tissue from reduction mammoplasties minced and dissociated in medium (See lines 1-4, right column, page 202, Stingl et al., 1998).

With regard to the isolated cell and the method of isolation of said cells, Stingl et al. teaches a method of isolation and characterization of *human breast epithelial cells (HBEC) with progenitor activity* by flow cytometry and single cell sorting to analyze the distribution of cellular phenotypes in primary cultures. Stingl et al. isolated two distinct types of HBEC progenitor populations to be distinguished on the basis of their differential expression of the MUC-1 glycoprotein, and epithelial-specific antigen (ESA). One type of HBEC progenitor populations is present in the MUC-$1^{-to\ +/-}$/ ESA^{+} subpopulation, which generated mixed colonies of both luminal and myoepithelial cells. When cultured in a collagen matrix, these *bipotent progenitors* generated large *branched colonies* composed of a heterogeneous population of cells, with some of the progeny cells expressing luminal epitopes (keratin 8/18, *keratin 19* and MUC-1) and others expressing myoepithelial epitopes (keratin 14 and CD44v6). The MUC-$1^{-to\ +/-}$/ ESA^{+} progenitors identified and characterized by Stingl et al. are candidate ductal progenitors *in vivo* (See abstract and introduction, Stingl et al., 1998).

However, Stingl et al. do not teach immortalization of distinct human mammary epithelial cell types by the expression of human papilloma virus E6 or E7 polypeptides.

At the time the claimed invention was made, immortalization of distinct human mammary epithelial cell types by the expression of human papilloma virus E6 or E7 polypeptides, was known in the art. For instance, Wazer et al. teach immortalization of distinct human mammary epithelial cell types by human papilloma virus 16 E6 or E7 (See title, Wazer et al., 1995).

With regard to claims 4, 6-13, and 15 of instant application, Wazer et al. teach (i) retroviral transfection of multiple mammary epithelial cell (MECs) by stable transfection of pLXSN (vector), pLXSN16E6 (HPV-16 E6), or pLXSNE7 (HPV-16, E7) to PA317 amphotrophic packaging cell lines (See Material and Methods, right column, page 3687, Wazer et al., 1995), and (ii) human papillomas virus 16 E6 and E7 oncogenes target p53 and Rb tumpr suppressor proteins, respectively, to immortalize MECs present in early or late passages of human mammary tissue-derived cultures or in milk (See abstract, Wazer et al. 1995). The immortalization step taught by Wazer et al. renders the MUC-$1^{-to\ +/-}$/ ESA^{+} progenitor cells immortalized, which preserve the abovementioned characteristic teach the MUC-$1^{-to\ +/-}$/ ESA^{+} epithelial progenitor cells.

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time of the invention to modify the isolated multipotent mammary epithelial cells by the teachings of Stingl et al. and introduce the HPV-16 E6 or HPV-16 E7 oncogene to the recited multipotent mammary epithelial cells to render the cells immortalized, by the teachings of Wazer et al. for therapeutic and/or investigative applications of these mammary epithelial progenitor cells.

One having ordinary skill in the art would have been motivated to modify the teachings of Stingl et al. by the teachings of Wazer et al. because the molecular characterization of the evolution of the cellular lineage in the human breast requires the ability to amplify the lineages to be studied.

There would have been a reasonable expectation of success given (i) the successful isolation of the MUC-$1^{-to\ +/-}$/ ESA^{+} progenitors identified and characterized by Stingl et al. being candidate ductal progenitors *in vivo* by the teachings of Stingl et al., and (ii) immortalization of distinct human mammary epithelial cell types by human papilloma virus 16 E6 or E7, and immortalization of normal human breast cells with either E6 or E7 did not lead to aberrant functional behavior in luminal or myoepithelial cells tested, by the teachings of Wazer et al. to develop a method for isolation and immortalization of human breast epithelial progenitor cells and conduct molecular characterization of the evolution of the cellular lineage in the human breast requires the ability to amplify the lineages of the isolated human breast epithelial progenitor cells by the method.

Thus, the claimed invention as a whole was clearly *prima facie* obvious.

Conclusion

6. No claim is allowed.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the

application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Any inquiry concerning this communication from the examiner should be directed to Wu-Cheng Winston Shen whose telephone number is (571) 272-3157 and Fax number is 571-273-3157. The examiner can normally be reached on Monday through Friday from 8:00 AM to 4:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the supervisory patent examiner, Peter Paras, can be reached on (571) 272-4517. The fax number for TC 1600 is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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